# EXHIBIT J

# An Investigation of Changes in Physical Properties of Injectable Calcium Hydroxylapatite in a Carrier Gel When Mixed with Lidocaine and with Lidocaine/Epinephrine

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INTRODUCTION As physicians incorporate calcium hydroxylapatite (CaHA) into their aesthetic treatment regimens, the question has arisen of whether the addition of anesthetic agents to prefilled CaHA syringes might provide sufficient anesthetic prophylaxis to warrant reduction in conventional anesthetic pretreatment procedures.

STUDY DESIGN Investigators sought to determine changes in the physical properties of CaHA induced by the addition of lidocaine and lidocaine with epinephrine into the prefilled CaHA syringe. The CaHA and gel carrier (CHM) were mixed with varying amounts of lidocaine and lidocaine with epinephrine to measure the number of passes back and forth for optimal homogeneity of lidocaine and CaHA in syringes, changes in viscosity, extrusion force, needle jam rates, elasticity, and pH.

RESULTS Ten mixing passes appeared sufficient for homogeneity. Viscosities and extrusion forces of CHM/lidocaine blends decrease with increasing amount of lidocaine. Needle jams do not increase. The pH and elasticity of the CHM/lidocaine blend are essentially equivalent to those of CHM alone. Epinephrine added to lidocaine did not alter the results enough to reach statistical significance.

CONCLUSIONS Addition of lidocaine to original CHM can be safely added without harmful changes in physical properties of the original soft tissue filler. Further studies are required to explore whether the addition of lidocaine to CHM alters patient discomfort, durability, and efficacy.

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Radiesse (BioForm Medical Inc., San Mateo, CA) is a soft tissue filler consisting of calcium hydroxylapatite (CaHA) microspheres, 25 to 45 μm in diameter, and a sodium carboxymethyl cellulose (CMC) carrier gel. Collectively, these two elements constitute the CaHA media, referred to herein as CHM. The filler is usually injected through a 25- to 27-gauge needle, 0.5 to 1.5 inches in length. Over a period of several weeks, the CMC is replaced by fibroblasts and extracellular matrix, leaving the CaHA microspheres in place to provide mechanical support.[1] Even though individual CaHA microspheres are radioopaque, moderate injection amounts do not disrupt most radiographic analysis.[2]

CHM is currently approved for treatment of severe facial folds and wrinkles, such as nasolabial folds, and for treatment of human immunodeficiency virus–associated facial lipoatrophy. Durability is estimated ranging from 10 to 18 months.[3–6] Additional uses of the product in the correction of marionette lines, oral commissures, prejowl sulcus, acne scarring, cheeks augmentations, infraorbital rim, and temporal hollows have been reported.[5,7–13]

Late in 2007, Busso and Applebaum[14] published a report of their experiences in combining CHM with lidocaine for off-label use of the soft tissue filler in treatment of the hand. In the report, Busso and Applebaum briefly explained how mixing the two compounds together appeared to considerably lessen discomfort in patients receiving a bolus of the mixture for hand rejuvenation and augmentation. Busso and Applebaum observed that 0.15 mL of 2% lido-

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caine per 1.3-mL syringe of CHM was the minimum amount of anesthetic that appeared to yield adequate anesthesia without excessive loss of physical properties. A number of other physicians are adopting the technique of Busso and Applebaum technique for mixing CHM with standard 2% lidocaine-HCl solutions, mixing between 0.05 and 0.40 mL of lidocaine with a 1.3-mL syringe of CHM.[15] Mixing 0.23 mL of 2% lidocaine solution with 1.3 mL of CHM yields 0.3% lidocaine concentration. This concentration is equivalent to that found in other soft tissue fillers, such as Zyderm and CosmoPlast.[16,17]

Not only do the individual volumes of lidocaine differ in this off-label application of CHM by physicians, but the mixing techniques are physician-specific as well. Some physicians draw the lidocaine directly into the syringe of CHM; others mix lidocaine and CHM with a nose-to-nose Luer-lok connector. Some physicians barely mix the lidocaine with CHM, while others mix to produce a homogenous media. The effects of these mixing techniques on the performance of CHM are unclear.

To characterize the effects of various lidocaine volumes and mixing techniques on CHM, the physical properties of CHM blended with 2% lidocaine-HCl solutions were measured. The results detailed below should help physicians better understand the properties of CHM mixed with lidocaine solutions.

## Study Purpose and Design

This study sought to characterize the physical properties of CHM combined with plain 2% lidocaine-HCl solutions and combined with 2% lidocaine-HCl solutions and 10 µg epinephrine—under various mixing conditions. Researchers studied a range of lidocaine concentrations, described below, to compare the dynamic viscosity, extrusion force, and needle jamming rate of the mixtures compared to those of commercially available CHM. Investigators also evaluated the dynamic viscosity of the mixtures at the front, middle, and back of each mixed syringe of lidocaine and CHM, as a measure of mixing efficiency. In addition, they compared the results of CHM mixed with lidocaine to those of CHM mixed with lidocaine and epinephrine.

### *Materials/Equipment*

CHM (Radiesse, BioForm Medical Inc) was commercially available material. The nominal fill volume per syringe was 1.3 mL as shown by product labeling. Testing was completed using from 3 to 12 different commercially available lots of CHM for each test condition.

The 2% lidocaine solution was composed of anhydrous lidocaine-HCl (20 mg/mL), NaCl (6 mg/mL), and methylparaben (1 mg/mL; Hospira, Lake Forest, IL). The 2% lidocaine solution with epinephrine was composed of anhydrous lidocaine-HCl (20 mg/mL), epinephrine (10 µg/mL), NaCl (6 mg/mL), sodium metabisulfite (0.5 mg/mL), citric acid (0.2 mg/mL), and methylparaben (1 mg/mL; Hospira).

A rheometer (Haake RS-600, Thermo-Fisher, Newington, NH) measured dynamic viscosity of the media. Extrusion force was measured by a materials tester (R5K Plus, Lloyd Instruments, Fareham, Hampshire, UK). Media pH was measured using a pH meter with a probe (Model 720A and SureFlow probe, respectively, Orion Instruments, Baton Rouge, LA). The female-to-female Luer-lok connectors used to connect the mixing and media syringes were Ark-Plas Part No. AP18FLXFEP (Flippin, AR).

### *Procedures*

During the course of the study and at each test condition, researchers examined a 1.3-mL syringe of CHM, mixed with one of four volumes of 2% lidocaine or 2% lidocaine plus epinephrine solution:

- 0.05 mL (0.07% final lidocaine-HCl);
- 0.10 mL (0.14% final lidocaine-HCl);
- 0.15 mL (0.21% final lidocaine-HCl);
- 0.23 mL (0.30% final lidocaine-HCl).

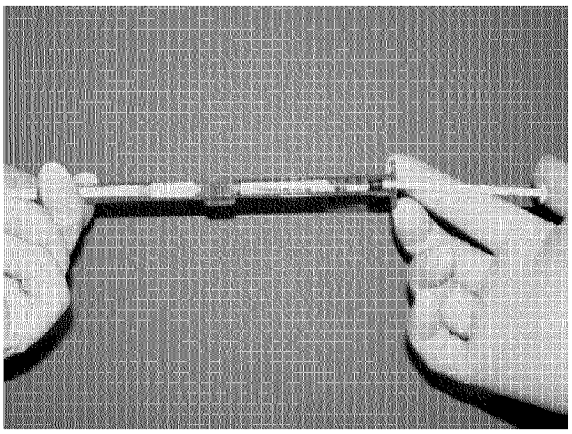

**Figure 1.** CHM mixed with lidocaine, using a female-to-female Luer-lok connector. (Photo courtesy of Mariano Busso, MD; used by permission of Blackwell Publishing Inc.)

Because the graduations on the tuberculin syringe are more accurate than those on a standard 1.3-mL syringe, the lidocaine solution was withdrawn from a 50-mL vial with a 1.0-mL tuberculin syringe (Becton Dickinson [B-D], Franklin Lakes, NJ) fitted with a 0.5-inch, 27-gauge B-D needle. The lidocaine solution was then injected from the tuberculin syringe into the nose of a BioForm 1.3 mL syringe (mixing syringe). The push rod of the mixing syringe was depressed to remove all excess air and then the mixing syringe with lidocaine was firmly connected to a syringe of CHM using a female-to-female Luer-lok connector (Figure 1).

Lidocaine and CHM were mixed by alternately depressing the plungers on the mixing and media syringes for 2, 5, or 10 mixing strokes. Each mixing stroke was composed of one complete compression of the CHM syringe push rod, followed by one complete compression of the mixing syringe push rod. Push rods were compressed firmly and quickly, at approximately two compressions per second. Following mixing, the mixing syringe and Luer-lok connector were removed and discarded, and the lidocaine/CHM mixture was recapped with the original media syringe cap. The CHM and lidocaine blends were tested between 15 minutes and 2 hours after mixing with lidocaine.

Nine rheology replicates, 12 extrusion force replicates, and at least three pH replicates were conducted per test condition. Rheology was evaluated with a 20-mm titanium rotor, with a gap of 2.0 mm and tau ($\tau$) of 5 N, over a frequency sweep of 0.1 to 10 Hz evaluated at 0.6 and 5.0 Hz. Extrusion force was evaluated through 27-gauge, 0.5-inch B-D needles, with an extension rate of 2 inches per minute. Media pH was obtained by completely coating the glass bulb of the pH probe with media, spreading or smoothing the media with a plastic spatula as necessary.

To evaluate the extent of mixing under different conditions, rheology and pH were tested for media from the front (hub), middle, or back (plunger) of the syringe barrel. Approximately 0.4 mL of media from the front, middle, or back of two syringes was combined for each measurement.

## Results

Investigators evaluated seven test conditions in the study: 1) number of passes between syringes sufficient for blending lidocaine and CHM; 2) changes in viscosity with differing concentrations of lidocaine; 3) extrusion forces of lidocaine and CHM, compared to CHM alone; 4) incidence of needle jamming in lidocaine/CHM blend; 5) pH of lidocaine/CHM compared to CHM alone; 6) viscosity and elasticity of CHM and lidocaine compared to CHM and lidocaine with epinephrine; and 7) extrusion force of CHM and lidocaine compared to CHM and lidocaine with epinephrine.

### *1. Number of Passes between Syringes Sufficient for Blending Lidocaine and CHM*

Figure 2 shows the percentage difference from the mean for the dynamic viscosity at 0.6 Hz under various mixing conditions. With "adequate mixing" defined as a percentage difference less than 10% for media across all regions of the syringe, 10 mixing passes provided adequate mixing for all lidocaine volumes tested. Five mixing passes provided adequate

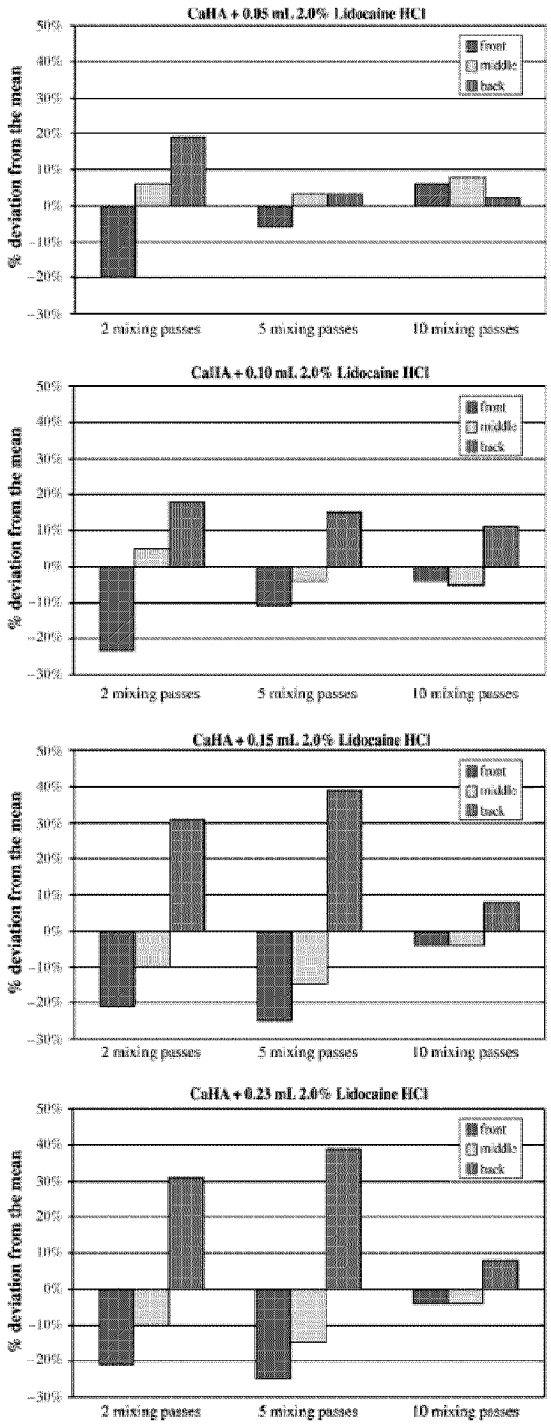


**Figure 2.** Percentage differences in distribution of four separate volumes of lidocaine with CHM, under three mixing conditions.

mixing for 0.05 mL of lidocaine solution, but not for the other volumes. Two mixing passes did not provide adequate mixing for any volume tested, with the net front-to-back spread ranging from 39% at 0.05 mL of lidocaine, up to 52% at 0.23 mL of lidocaine.

The magnitude of the front-to-back difference in viscosity increased with increasing volume of lidocaine, suggesting that larger volumes of lidocaine required more mixing than small volumes, but also reflecting a greater magnitude of change in physical properties with increasing concentration of lidocaine. Profiles of the extrusion force versus syringe extension also demonstrated that 10 mixing strokes were adequate to homogeneously mix the CHM and lidocaine solution (Figure 3).

Following 10 mixing strokes, the extrusion force was uniform from the front to the back of the syringe, even at the maximum tested volume of lidocaine. In contrast, the front extrusion force was much lower than the back extrusion force for syringes blended with 2 or 5 mixing strokes, and the front of the syringe exhibited numerous jagged troughs, indicating the presence of air bubbles in the syringe.

### *2. Changes in Viscosity with Differing Concentrations of Lidocaine*

Viscosities of CHM/lidocaine blends decreased with increasing lidocaine HCl. As shown in Figure 4, the dynamic viscosity of CHM/lidocaine blends was inversely proportional to the volume of lidocaine-HCl solution ($R^2 = 0.99$). Even at 0.23 mL of lidocaine HCl, the CMC gel was cohesive enough to suspend the particles for the 24-hour testing period (Figure 4).

### *3. Extrusion Forces of Lidocaine and CHM Blend, Compared to CHM Alone*

The extrusion forces of CHM/lidocaine blends were lower than those of CHM alone (Figure 5). The extrusion force through a 27-gauge, 0.5-inch B-D needle was nearly constant around 5.3 pounds of force (lbf) for CHM blended with 0.05, 0.10, or 0.15 mL lidocaine-HCl, down from 6.0 lbf for CHM

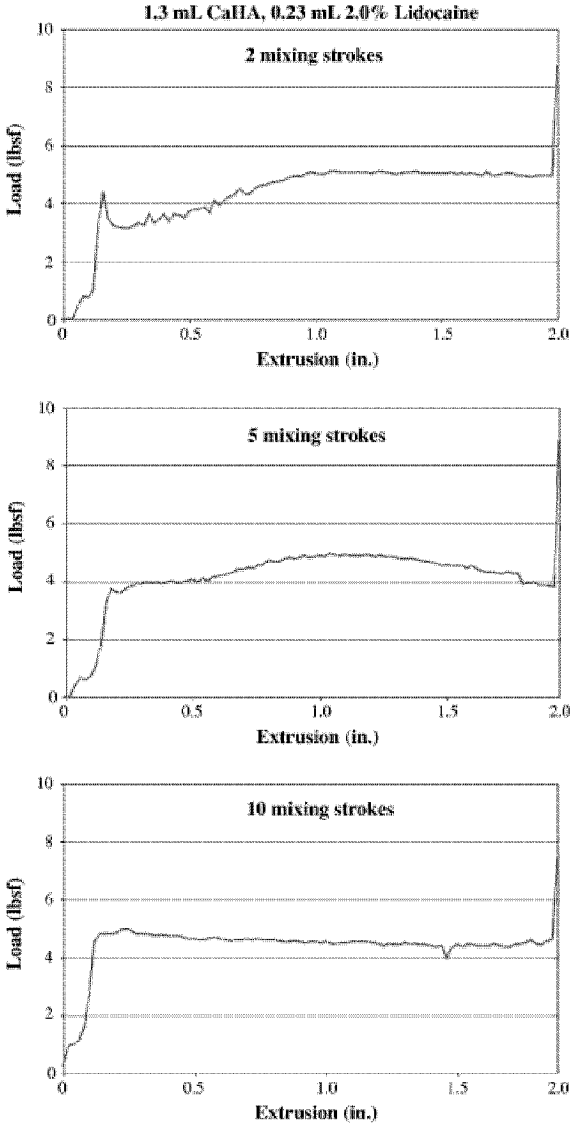


**Figure 3**. Force versus extension of CaHA with 0.23 mL lidocaine (0.3%).

alone. Extrusion force decreased to 4.7 lbf for 1.3 mL CHM with 0.23 mL 2% lidocaine solution.

### *4. Incidence of Needle Jamming in Lidocaine/CHM Blend*

Blending CHM with lidocaine did not increase the incidence of needle jamming. Twelve extrusions were performed for each of the seventeen experimental

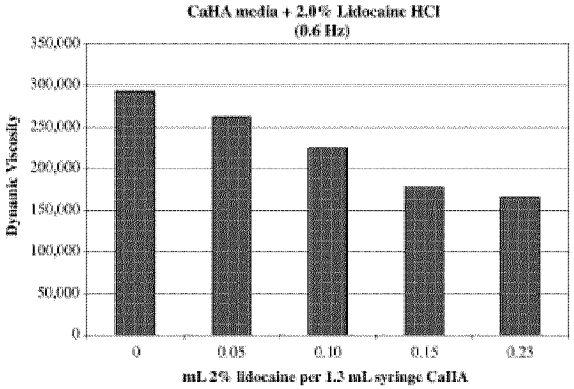


**Figure 4**. Dynamic viscosity of CHM blended with various volumes of 2% lidocaine-HCl.

conditions, for a total of 204 extrusions. Only two needle jams were observed among these extrusions, for an estimated jam rate of 0.98%. This jam rate is comparable to the jam rate observed for CHM.[18]

### *5. Elasticity and pH of Lidocaine/CHM Compared to CHM Alone*

Elasticity is a qualitative term, while G′, G, and tan (δ) are quantitative measures of how vigorously a material bounces back to its initial position following a stress or strain. The elasticity of CHM and lidocaine blends decreased with increasing concentration of lidocaine mixes (Figure 6). The tan delta (δ) values (the tangent of the ratio of loss modulus [G] over the storage modulus [G′]) provides a

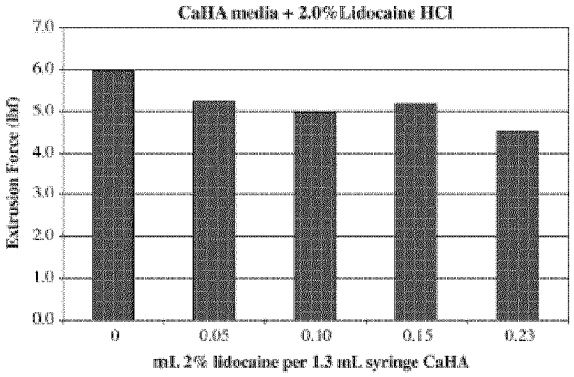


**Figure 5**. Extrusion force, CHM blended with various volumes of 2% lidocaine-HCl.

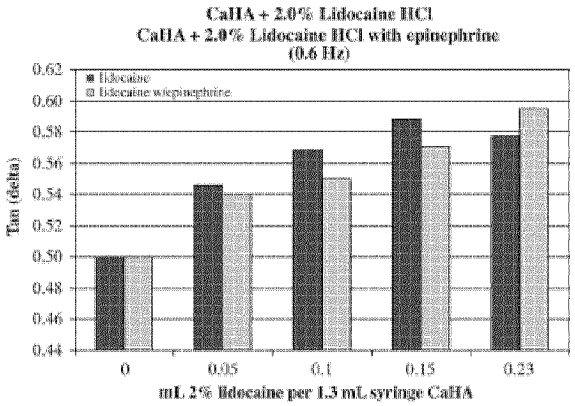


**Figure 6.** Tan (δ), CHM blended with various volumes of 2% lidocaine-HCl.

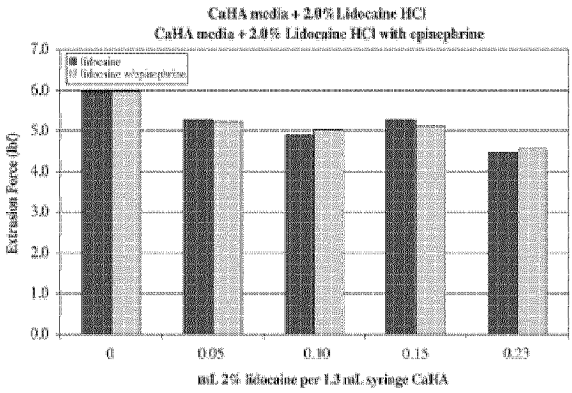


**Figure 8.** Extrusion force of CHM and lidocaine compared to CHM and lidocaine with epinephrine.

quantitative tool to evaluate the relative elasticity of the media. CHM and lidocaine blends were less elastic than CHM alone. The pH of all CHM and lidocaine blends was between 6.6 and 7.2 for all samples.

### *6. Dynamic Viscosity of CHM Compared to CHM and Lidocaine with or without Epinephrine*

Dynamic viscosity measures the way a fluid responds to stresses and strains. Dynamic viscosity decreased with the increasing volume of lidocaine solution added to 1.3 mL CHM (Figure 7). There was a trend toward higher viscosity for lidocaine with epinephrine versus lidocaine only. However, statistical

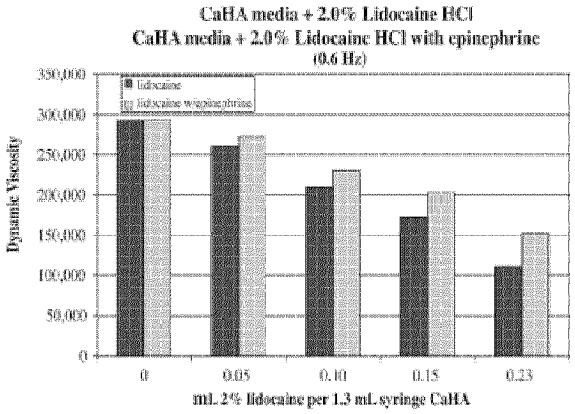


**Figure 7.** Dynamic viscosity, CHM blended with various volumes of 2% lidocaine-HCl.

significance in viscosity differences ($p<.05$) was only seen with the 0.15- and 0.23-μL additions to lidocaine/epinephrine solution volumes.

### *7. Extrusion Force of CHM and Lidocaine Compared to CHM and Lidocaine with Epinephrine*

Extrusion force decreased with the increase in volume of lidocaine solution added to 1.3 mL CHM (Figure 8). Although the extrusion force was found to be slightly lower with the addition of lidocaine with epinephrine, the difference was not statistically significant. At all volumes of lidocaine, the extrusion force was essentially equivalent for CHM blended with lidocaine and CHM blended with lidocaine/epinephrine, suggesting that epinephrine had no effect on extrusion force.

## Discussion

Mixing lidocaine with CHM does not compromise the physical properties of the original soft tissue filler. The viscosity of the gel in CHM and lidocaine blends is sufficient to keep the CaHA particles in suspension and prevent needle jams after dilution with 2% lidocaine solutions. The pH values of CHM and lidocaine blends are functionally equivalent to those of CHM alone. In addition, blending CHM with lidocaine reduces viscosity and extrusion force, and for physicians who wish to add epinephrine to

the lidocaine used in the CaHA/lidocaine mix, there is no substantial change in viscosity properties in the epinephrine/lidocaine combination compared to lidocaine alone. We proved that 10 mixing strokes of the CaHA and carrier gel with various amounts of lidocaine are necessary for homogeneity.

CaHA has been approved essentially for "bulking" applications. A bulking filler is characterized by minimum lateral implant leakage. In this study, the changes in rheology, viscosity, extrusion, and pH suggest that CaHA/CMC has even broader applications. Anatomic areas like temples, preauricular space, and dorsum of the hand benefit from having "malleability" or "spreadability" of the product with the addition of lidocaine and reduction of viscosity. By altering the viscosity, the physician can more easily inject the product in layers, criss-crossing the junction of the dermal/subdermal plane or a bolus followed by a blending massage.

The combination of lidocaine and CaHA intuitively suggests, as do anecdotal reports, that patient discomfort levels will likely be reduced during injection of the product. One example of the decrease in patient discomfort is the treatment of the hand with a bolus of CaHA. With the addition of lidocaine (and perhaps epinephrine) to the CaHA, physicians have increased flexibility in their treatment techniques and sites of injection, and the benefits of decreased patient discomfort.

From a physiologic properties perspective, the findings of the study provide scientific data to physicians who are engaging in off-label mixing of lidocaine and/or lidocaine and epinephrine with CHM. The pH stays within physiologically safe ranges, the viscosity and extrusion forces decrease, and CHM and the anesthetic agent(s) are adequately mixed with 10 back-and-forth passes of anesthetic into CHM. The benefits to physicians who choose to mix lidocaine with CHM may include: reduction of confounding edema secondary to pretreatment infiltration with lidocaine, increased ease in molding, increased comfort to the patient, reduced need for nerve blocks, and decreased treatment times. Altogether, these benefits allow larger volumes to be injected in one treatment session, such as those necessary for full facial recontouring.

Answers to several other questions about the mixing process were beyond the scope of the study and remain unknown. The study did not address the anesthetic efficacy of lidocaine following prolonged contact with CHM. Since CMC is a known time-release agent for lidocaine-HCl[19] and CaHA is a well-known controlled release agent for many drugs,[20–23] a significant time delay between mixing media with lidocaine and injection could have undesirable effects on anesthetic efficacy. Consequently, physicians may have to rely on their best clinical judgments and anecdotal evidence as they consider the addition of lidocaine to the prefilled syringe of CHM. In addition, the mixing of a sterile product with lidocaine increases the risk of microbial contamination and any storage of opened CHM is not recommended.

The question could be raised about whether these results represent merely a 10% to 15% dilution factor or whether there are other chemical changes in lidocaine/vehicle interactions, for example, whether other bonds be disrupted by the addition of lidocaine. CaHA and CMC are both known to adsorb drugs without chemically altering them; there is no reason to anticipate that they would behave differently toward lidocaine. Further studies are needed to confirm the hypothesis of no chemical alterations.

This study also does not address the effect of lidocaine on in vivo duration of the clinical benefits of CHM. Physicians have reported that they see no significant decrease in durability for media diluted with lidocaine. However, the test condition of a 0.23-mL lidocaine dose (0.3% concentration of lidocaine) represents a 15% dilution of CMC and microspheres, by volume—a larger lidocaine volume than the 0.10-mL lidocaine dose described in the original study by Busso and Applebaum. Without answers to possible dilution of anesthetic properties

and shortening or extending durability of the soft tissue filler, the manufacturers of CHM rely on the judgment of the treating physician to include the mixing of CHM with lidocaine solutions into their practice. Controlled animal or clinical trials would be required to prove that dilution of CHM with lidocaine does not adversely affect product durability. The benefits of using CHM with lidocaine with the lower viscosity, lower extrusion force, greater ease of molding, and increased patient comfort may be attractive to healthcare providers who use CHM in their daily practice.

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## COMMENTARY

The authors are to be commended for an excellent study. In the practice of medicine, many times products are adulterated based on anecdotal information passed from physician to physician. Without appropriate studies, we as clinicians have no way of knowing if these adulterations may have a negative impact on the product. This article exhaustively examines and puts to rest any concerns about harmful changes to the physical properties of injectable calcium hydroxylapatite (CaHA) when mixed with lidocaine.

It remains to be seen if this combination has any negative effect on the efficacy or duration of effect of injectable CaHA. There is no question the addition of lidocaine makes the injection of this material markedly more comfortable, as well as allowing more aggressive massage of the treated area. In addition, it allows the clinician to avoid a nerve block, thereby speeding up the procedure and sparing the patient the edema and profound anesthesia associated with the block.

Hopefully further studies will appear documenting the efficacy of this mixture. Until then, many clinicians, including myself, will continue to use this mixture based on our observation that its efficacy and duration seem unaffected by the addition of lidocaine.

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